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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/730,790	12/05/2000	Mark H. Tuszynski	041673/2047	8867

30542 7590 02/19/2004

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 02/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/730,790	TUSZYNSKI ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *6,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of group I, claims 1-5, 7, 8 and 11-15, in the response filed 8-13-03 is acknowledged.

2. Claims 6, 9 and 10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response filed 8-13-03.

Claims 1-15 are pending and claims 1-5, 7, 8 and 11-15 are under consideration.

Specification

3. The disclosure is objected to because of the following informalities: The term "Claims" on page 23 is improper. Changing the term "Claims" to "What is claimed is:" or "We claim" would be remedial.

Appropriate correction is required.

4. The disclosure is objected to because of the following informalities: A clean substitute page(s) reflecting the amendment filed 4-18-01 regarding the "Brief Description of Drawings" contained on pages 3 and 4 has not been submitted accompanying said amendment. Submission of the clean substitute page(s) is required.

Appropriate correction is required.

Priority

The present application claims priority of Application No. 09/060,543, filed 4-15-98, however, Application No. 09/060,543 fails to disclose a method for ameliorating neuronal

atrophy and loss accompanying normal aging in the mammalian brain by delivering a transgene encoding a growth factor to preselected sites in the brain. Therefore, the claimed priority of Application No. 09/0606,543 is not granted. The priority date of the present invention is the actual filing date of the present application, i.e. 12-5-00.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-3, 5, 7, 8 and 11-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7 and 11-17 of U.S. Patent No. 6,683,058 ('058). Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 1-3, 5, 7, 8 and 11-15 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor, such as NGF or neurotrophin 3, to preselected sites in the brain, for example the targeted cholinergic neurons are

within 500 um of a delivery site, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

Claims 1, 2, 7, and 11-17 of '058 are directed to a method for delivery of a therapeutic neurotrophin to targeted defective, diseased or damaged cholinergic neurons in a mammalian brain comprising delivering a neurotrophic composition comprising a transgene, such as NGF or neurotrophin 3, or a viral expression vector encoding a neurotrophin into one or more sites within the targeted regions of a mammalian brain, wherein the neurotrophin is expressed in, or within 500 um from, a targeted cell, and no more than about 10 mm from another delivery site, to ameliorate the defect, disease or damage, such as Alzheimer's disease, *in vivo*.

The growth factor encoding transgene of the present invention encompasses the neurotrophin encoding transgene of '058 and neurotrophin is a type of growth factor, therefore, the claimed invention of the present application would be obvious for one of ordinary skill at the time of the invention according to the teachings of '058.

7. Claims 1-3, 5, 7, 8 and 11-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 7, 9-15 and 19 of copending Application No. 10/032,952. Although the conflicting claims are not identical, they are not patentably distinct from each other because although drawn to different scope, they encompass the same invention and obvious variants thereof.

Claims 1-3, 5, 7, 8 and 11-15 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor, such as NGF or

neurotrophin 3, to preselected sites in the brain, for example the targeted cholinergic neurons are within 500 um of a delivery site, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

Claims 1, 7, 9-15 and 19 of application No. 10/032,952 are directed to a method for delivery of a therapeutic neurotrophin to targeted defective, diseased or damaged neurons in a mammalian brain comprising directly delivering a neurotrophic composition comprising an expression vector encoding a neurotrophin, such as NGF, GDNF or neurotrophin 3, into one or more sites within the targeted mammalian brain, wherein the neurotrophin is expressed in a cell that is, or is in proximity to, or within 500 um from, a defective, diseased or damaged neuron *in vivo*.

The growth factor encoding transgene of the present invention encompasses the neurotrophin encoding transgene of application No. 10/032,952 and neurotrophin is a type of growth factor, therefore, it would be obvious for one of ordinary skill at the time of the invention to deliver a growth factor encoding gene to the mammalian brain according to the teachings of 10/032.952. Further, the teaching of application No. 10/032,952 to have the neurotrophin expressed in, or in proximity to, the defective, diseased or damaged neuron would make it obvious for one of ordinary skill in the art to deliver the growth factor encoding transgene to a preselected delivery site so as to stimulate axonal growth in targeted neurons.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 7, 8 and 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the disclosure by Mandel et al., 1999 and Felgner et al., 1996, as discussed below, does not reasonably provide enablement for a method for ameliorating neuronal atrophy and loss accompanying normal aging in a mammalian brain by administering a growth factor encoding transgene in any vector to a preselected delivery site in the brain via various administration routes in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-5, 7, 8 and 11-15 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor, such as NGF or neurotrophin 3, to preselected sites in the brain, for example the targeted cholinergic neurons are within 500 um of a delivery site or more than 500 um of a delivery site, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

The specification discloses intraparenchymal delivery of genetically modified fibroblast cells expressing human NGF to monkey brain and shows significant reversal of age-related

decline in cortical cholinergic innervation. The claims encompass delivering any growth factor encoding transgene in any vector via various administration routes to a mammalian brain such that therapeutic effect could be obtained to ameliorate neuronal trophy and loss accompanying normal aging in said mammalian brain in vivo.

The specification fails to provide adequate guidance and evidence for how to deliver any growth factor encoding trasngene in any vector to a mammalian brain via various administration routes, such as systemic administration or administration at a site distant from the brain, so as to provide therapeutic effects and to ameliorate neuronal atrophy and loss accompanying normal aging in said mammalian brain *in vivo*.

The claims read on gene therapy *in vivo*. Grafting cells secreting NGF into a mammalian brain is different from administering transgene into a mammalian brain. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., 1997 (Nature, Vol. 389, pages 239-242) reports that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus, far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (see page 239, right column). Verma also teaches appropriate

regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). Administration route of a transgene to a subject palys an important role in determining the efficiency of gene transfer in vivo

It also was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post

mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to administer any growth factor encoding transgene in any vector to a mammalian brain via various administration routes so as to provide therapeutic effects and to ameliorate neuronal atrophy and loss accompanying normal aging in said mammalian brain *in vivo*.

The specification also fails to provide adequate guidance for whether administration of any growth factor encoding transgene to a mammalian brain would provide therapeutic effect in vivo so as to ameliorate neuronal atrophy and loss accompanying normal aging in the brain. Growth factor is a very broad term that composes a group of diverse protein molecules that regulate cell growth, differentiation, and cell-cell communications. Growth factor includes vitamin B12, growth hormones, IL-2, IL-4, GCSF, CNTF, IL-1alpha, IL-1beta, FGF, EGF and TGF-alpha etc. Different proteins have different biological functions. The mechanisms that govern growth factor-mediated processes were largely unknown at the time of the invention. There is no evidence of record that a growth factor that regulates cell differentiation, cell-cell communication or even cell growth could ameliorate neuronal atrophy and loss accompanying

normal aging in the mammalian brain in vivo. Thus, one skilled in the art at the time of the invention would not know how to use those various growth factor encoding transgene to ameliorate neuronal atrophy and loss accompanying normal aging in the mammalian brain in vivo.

For the reasons set forth above, it would have required one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1, 2, 5, 7, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Mandel et al., 1999 (Experimental Neurology, Vol. 155, No. 1, pp. 59-64).

Claims 1, 2, 5, 7, 11, 12, 14 and 15 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor, such

as human NGF, to preselected sites in the brain, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

Mandel teaches generation of a recombinant adeno-associated viral (AAV) vector comprising a human NGF cDNA and direct administration of said recombinant AAV vector to fimbriafornix (FF) lesion in rats, and shows said recombinant AAV vector significantly attenuate the medial septal cholinergic cell loss as compared to control rAAV vector (e.g. abstract). AAV vector is a viral vector. Therefore, claims 1, 2, 5, 7, 11, 12, 14 and 15 are anticipated by Mandel.

3. Claims 1, 2, 5, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticpated by Felgner et al., 1996 (US Patent No. 5,580,859).

Claims 1, 2, 5, 11, 12, 14 and 15 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector comprising a transgene encoding a growth factor, such as human NGF, to preselected sites in the brain, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

Felgner teaches introduction of a DNA encoding neuronal growth factor into targeted cholinergic neurons in the medial septum by using stereotaxic apparatus for the treatment of Alzheimer's disease (e.g. column 16). Thus, claims 1, 2, 5, 11, 12, 14 and 15 are anticipated by Felgner.

4. Claims 1, 5 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Kojima et al., 1997 (Biochemical and Biophysical Research Communications, Vol. 238, p. 569-573, IDS-A1).

Claims 1, 5 and 7 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor to preselected sites in the brain, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron.

Kojima teaches preparation of a recombinant adenoviral vector comprising a human glial cell-line derived neurotrophic factor (hGDNF) and demonstrates that administration of said recombinant adenoviral vector to mouse brain prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine0induced dopamine depletion in striatum of said mouse brain (e.g. title, abstract). Thus, claims 1, 5 and 7 are anticipated by Kojima.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandel et al., 1999 (Experimental Neurology, Vol. 155, No. 1, pp. 59-64).

Claims 1, 5, 7 and 8 are directed to a method for ameliorating neuronal atrophy and loss accompanying normal aging in the mammalian brain by delivering as expression vector, such as a viral vector, comprising a transgene encoding a growth factor to preselected sites in the brain, wherein the encoded growth factor is expressed and stimulates axonal growth in targeted neuron, such as cholinergic neurons.

Mandel teaches generation of a recombinant adeno-associated viral (AAV) vector comprising a human NGF cDNA and direct administration of said recombinant AAV vector to fimbriafornix (FF) lesion in rats, and shows said recombinant AAV vector significantly attenuate the medial septal cholinergic cell loss as compared to control rAAV vector (e.g. abstract). Mandel also teaches using $1.7x10^{12}$ rAAV-MFG-hNGF viral particles/ml and $1.0x10^{12}$ rAAV-CMV-LacZ for gene transfer of the human NGF to cholinergic neurons in the medial septum (e.g. page 60, left column first paragraph).

Mandel does not specifically teach using 10^{10} to 10^{12} viral particles/ml expressing growth factor for gene transfer to the mammalian brain.

It would have been obvious for one of ordinary skill in the art at the time of the invention to administer $1.0x10^{10}$ to $1.0x10^{12}$ viral particles/ml expressing growth factor to the mammalian brain because Mandel teaches administering $1.7x10^{12}$ rAAV-MFG-hNGF viral particles/ml and

$1.0x10^{12}$ rAAV-CMV-LacZ (control) for gene transfer of the human NGF to cholinergic neurons in the medial septum. Determining effective dose is routine optimization of a result-effective variable and is obvious to a person of ordinary skill.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to determine whether administration of a recombinant AAV vector expressing a human NGF would significantly attenuate the medial septal cholinergic cell loss as taught by Mandel with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.